Docket No.: 30694/41506
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kollet et al.

Application No.: 10/552,299

Filed: August 25, 2006

For: Stem Cells Having Increased Sensitivity to SDF-1 and Methods of Generating and Using Same

Confirmation No.: 2069

Art Unit: 1632

Examiner: Shen, Wu Cheng Winston

PETITION TO WITHDRAW HOLDING OF FINALITY PURSUANT TO 37 C.F.R. § 1.181, M.P.E.P. § 706.07(C)-(G) AND M.P.E.P. § 1002.02(C)

MS Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §1.181, Applicants request that the finality of the January 20, 2010, Office Action be withdrawn. This request and petition is timely filed under 37 C.F.R. §1.181, M.P.E.P. §706.07(c)-(g) and M.P.E.P. §1002.02(c) within two months of the date of the Office Action. Applicants believe no fee is due with the filing of this petition; however, the Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees required in connection with the filing of this petition to Deposit Account No. 13-2855, under Order No. 30694/41506.

Statement of Facts begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

STATEMENT OF FACTS IN SUPPORT OF PETITION

1. On May 27, 2009, the Examiner issued a first Office Action setting forth a rejection of claims 30-36, 38, and 39 under 35 U.S.C. § 112, second paragraph, as assertedly indefinite. The Examiner objected to the term "a predetermined threshold" in claim 30 because the specification allegedly did not define the term. See page 4 of the Office Action mailed May 27, 2009. Claims 31-36, 38, and 39 depend from claim 30.

2. In that first Action, the Examiner also rejected claims 30-36, 38, and 39 under 35 U.S.C. § 102(b). The rejections were as follows: (1) claims 30-36, 38, and 39 were rejected as assertedly being anticipated by Kollet et al., *Blood*, 97(10):3283-91 (2001) as evidenced by Janowska-Wieczorek et al., *Blood*, 93(10):3379-90) (1999), (2) claims 30-36, 38, and 39 were rejected as assertedly being anticipated by Kollet et al., *Exp. Hematol.*, 28(6):726-36 (2000) as evidenced by Janowska-Wieczorek et al., *Blood*, 93(10):3379-90 (1999). The claims pending at the time of the first action are attached hereto as Exhibit A.

3. In remarks provided in the first Office Action mailed May 27, 2009, the Examiner expressly stated that "[t]he limitation 'exposing said stem cells to a matrix metalloprotease or an active portion thereof' recited in claim 30 reads on exposure to (i) any amount of a matrix metalloprotease expressed by either exogenous or endogenous nucleic acid molecule of collected stem cells, or (ii) any amount of matrix metalloprotease polypeptide added exogenously to the collected stem cells." See Office Action mailed May 27, 2009, at p. 6.

4. On October 12, 2009, Applicants filed a response traversing the rejections and amending claims 30, 38 and 39. The claims as amended in the response are attached hereto as Exhibit B. Claim 30 was amended to refer to an "exogenous" matrix metalloprotease and the isolating step was amended to CXCR4 having increased levels "compared to stem cells not exposed to the matrix metalloprotease or active portion thereof." Claims 38 and 39, each of which depends from claim 30, were amended to conform to the amendment of claim 30.

5. Specifically, claim 30, as amended in the Applicants' response of October 12, 2009, reads as follows:

> 30. (Currently amended) A method of generating stem cells suitable for transplantation, the method comprising:

(a) collecting stem cells;

(b) exposing said stem cells to ~~a~~ an exogenous matrix metalloprotease or an active portion thereof; and

(c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof~~above a predetermined threshold~~, to thereby generate stem cells suitable for transplantation.

6. On January 20, 2010, the Examiner issued a second Office Action, which was designated "final" and is the subject of this petition. The Examiner withdrew the various rejections under 35 U.S.C. § 102(b) and §112, second paragraph, and set forth a new rejection of claims 30-36, 38 and 39 under 35 U.S.C. §103(a) as assertedly obvious over Kollet et al., *Blood*, 97(10):3283-91 (2001), in view of Heissig et al., *Cell*, 109(5):625-37 (2002), Rafii et al., U.S. Patent Publication No. 2004/0071687, Togawa et al., *Cancer Lett.*, 146(1):25-33 (1999), and Sadatmansoori et al., *Protein Expr. Purif.*, 23(3):447-52 (2001). The Examiner issued the final Office Action on the stated basis that "*This rejection is necessitated by claim amendments filed on 10/12/2009*" (emphasis in original). Office Action of January 10, 2010, at p. 5.

REMARKS IN SUPPORT OF THE PETITION

The finality of the January 20, 2010, Office Action (hereinafter "the final Office Action") should be withdrawn because the Examiner raised new rejections under 35 U.S.C. §103(a), both of which could have been presented in the non-final Office Action mailed May 27, 2009 (hereinafter "the non-final Office Action"). The new rejections were not necessitated by Applicants' amendments. The reasons for the withdrawal of finality are discussed in further detail below.

I. The 35 U.S.C. § 103(a) rejections presented in the final Office Action could have been presented in the non-final Office Action.

The final Office Action alleged that Applicants' amendments caused new grounds for rejection under Section 103(a), and thus the second Office Action was made final. Applicants disagree. Claims 38 and 39, each dependent on claim 30, were amended to conform to the amended language of claim 30. Thus, in addressing the amendments of October 12, 2009, focus is properly placed on the two above-indicated amendments to claim 30 (i.e., use of an exogenous matrix metalloprotease and comparison of increased CXCR4 expression in the presence versus absence of the metalloprotease).

The first amendment added the limitation that the matrix metalloprotease (or active portion thereof) be exogenous. In the sole claim rejection in the outstanding final Office Action, the Examiner relied on Kollet, Heissig, Rafii, Togawa and Sadatmansoori, but the Examiner did not cite any of these references as disclosing or suggesting an exogenous matrix metalloprotease. Based on the failure to rely on any cited reference as disclosing or suggesting the "exogenous" matrix metalloprotease of the amended claims, it cannot be true that so amending the claims necessitated the admittedly new rejection imposed in the outstanding final Office Action.

Any rejection of claim 30 "necessitated" by these amendments could properly have been raised in the first Office Action. M.P.E.P. §706.07(a) provides that "[a] second or any subsequent action on the merits in any application or patent involved in reexamination proceedings should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be

claimed." In this instance, the Examiner should have reasonably expected Applicants to amend the claims to include the limitation "exogenous." Applicants further submit that the Examiner did expect the claims to be amended to recite an "exogenous" matrix metalloprotease. At page 6 of the previous (non-final) Office Action mailed May 27, 2009, the Examiner stated that "exposing said cells to a matrix metalloprotease or an active portion thereof," as recited in the then-pending claims, read on any amount of exogenous or endogenous matrix metalloprotease. The express statement is an admission that the claims pending prior to the amendment of October 12, 2009. could have been rejected over art disclosing or suggesting, *inter alia*, exogenous matrix metalloprotease. Thus, it was improper for the Examiner make an initial rejection of claims 30-36, 38 and 39 under Section 103(a) over Kollet in view of Heissig, Rafii, Togawa and Sadatmansoori in an Office Action that the Examiner made final.

The second amendment to claim 30 clarified the scope of the claimed subject matter. The Examiner rejected claim 30 under 35 U.S.C. § 112, second paragraph, as indefinite in reciting a "predetermined threshold" without adequate definition of the threshold. In response, Applicants defined the threshold as an increase in CXCR4 levels in the presence versus the absence of the matrix metalloprotease. Again, the Examiner did not rely on any of the references cited in the outstanding final Office Action as disclosing or suggesting this element of the amended claim.

For the foregoing reasons, the Examiner has not established a proper basis for making the instant Office Action final, and Applicants request that the finality of the outstanding Office Action mailed January 20, 2010, be withdrawn.

II. Conclusion

In view of the arguments set forth above, the finality of the January 20, 2010, Office Action is improper and should be withdrawn. A withdrawal of the finality of the Office Action is respectfully requested.

Dated: March 17, 2010

Respectfully submitted,

By _____

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EXHIBIT A

Listing of claims pending at time of first Office Action:

1. (Withdrawn) A method of increasing sensitivity of stem cells to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

2. (Withdrawn) The method of claim 1, wherein said at least one chemoattractant receptor is CXCR4.

3. (Withdrawn) The method of claim 1, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

4. (Withdrawn) The method of claim 1, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

5. (Withdrawn) The method of claim 1, wherein the stem cells are hematopoietic stem cells.

6. (Withdrawn) The method of claim 5, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

7. (Withdrawn) The method of claim 6, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

8. (Withdrawn) The method of claim 1, wherein the stem cells are mesenchymal stem cells.

9. (Withdrawn) The method of claim 1, wherein said exposing the stem cells to said matrix metalloprotease or said active portion thereof, is effected by:

(i) expressing a polynucleotide encoding said matrix metalloprotease or an active portion thereof in the stem cells; and/or

(ii) contacting the stem cells with said matrix metalloprotease or an active portion thereof.

10. (Withdrawn) A method of treating a disorder requiring cell or tissue replacement, the method comprising providing to a subject in need thereof a therapeutically effective amount of stem cells treated with a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells, thereby treating the disorder requiring cell or tissue replacement in the subject.

11. (Withdrawn) The method of claim 10, wherein said at least one chemoattractant receptor is CXCR4.

12. (Withdrawn) The method of claim 10, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

13. (Withdrawn) The method of claim 10, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

14. (Withdrawn) The method of claim 10, wherein the stem cells are hematopoietic stem cells.

15. (Withdrawn) The method of claim 14, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

16. (Withdrawn) The method of claim 15, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

17. (Withdrawn) The method of claim 10, wherein said stem cells are mesenchymal stem cells.

18. (Withdrawn) A culture medium suitable for increasing the sensitivity of stem cells to a chemoattractant, the culture medium comprising a matrix metalloprotease or an active portion thereof which is capable of increasing a level of at least one chemoattractant receptor of the stem cells and a buffer solution suitable for stem cell culturing.

19. (Withdrawn) The culture medium of claim 18, further comprising a differentiation inhibiting factor.

20. (Withdrawn) The culture medium of claim 18, further comprising serum or serum replacement.

21. (Withdrawn) The culture medium of claim 18, further comprising an agent selected from the group consisting of SCF, HGF and IL-6.

22. (Withdrawn) Use of a matrix metalloprotease or an active portion thereof for the manufacture of a medicament for increasing homing of stem cells to a target tissue.

23. (Withdrawn) The use of claim 22, wherein said stem cells are hematopoietic stem cells.

24. (Withdrawn) The use of claim 23, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

25. (Withdrawn) The use of claim 24, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

26. (Withdrawn) The use of claim 22, wherein said stem cells are mesenchymal stem cells.

27. (Withdrawn) The use of claim 22, wherein said target tissue is selected from the group consisting of bone marrow, blood vessel, heart, lung, liver, pancreas, kidney, nervous system, skin, bone and skeletal muscle.

28. (Withdrawn) The use of claim 22, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

29. (Withdrawn) The method of claim 22, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

30. (Original) A method of generating stem cells suitable for transplantation, the method comprising:

(a) collecting stem cells;

(b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and

(c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation.

31. (Original) The method of claim 30, wherein collecting said stem cells is effected by:

(i) a stem cell mobilization procedure; and/or

(ii) a surgical procedure.

32. (Original) The method of claim 30, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

33. (Original) The method of claim 30, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

34. (Original) The method of claim 30, wherein said stem cells are hematopoietic stem cells.

35. (Original) The method of claim 34, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

36. (Original) The method of claim 34, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

37. (Withdrawn) The method of claim 30, wherein said stem cells are mesenchymal stem cells.

38. (Original) The method of claim 30, wherein said exposing said stem cells to said matrix metalloprotease or said active portion thereof, is effected by:

(i) expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells; and/or

(ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof.

39. (Original) The method of claim 30, wherein said isolating stem cells having CXCR4 levels above said predetermined threshold is effected by FACS.

40. (Withdrawn) The method of claim 31, further comprising determining homing capabilities of said stem cells having CXCR4 levels above said predetermined threshold following step (c).

41. (Withdrawn) A nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloportease or an active portion thereof and an inducible cis-acting regulatory element for directing expression of said polynucleotide in cells.

42. (Withdrawn) The nucleic acid construct of claim 41, wherein said inducible cis-acting regulatory element is a shear stress activation element.

43. (Withdrawn) The nucleic acid construct of claim 41, further comprising a second polynucleotide sequence being translationally fused to said first polynucleotide sequence, said second polynucleotide sequence encoding a signal peptide capable of directing secretion of said matrix metalloportease or said active portion thereof out of said cells.

44. (Withdrawn) The nucleic acid construct of claim 41, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

45. (Withdrawn) The nucleic acid construct of claim 41, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

46. (Withdrawn) A eukaryotic cell comprising the nucleic acid construct of claim 41.

47. (Withdrawn) A cell-line comprising stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease.

48. (Withdrawn) The cell-line of claim 47, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

49. (Withdrawn) The cell-line of claim 47, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

50. (Withdrawn) The cell-line of claim 47, wherein said stem cells are hematopoietic stem cells.

51. (Withdrawn) The cell-line of claim 50, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

52. (Withdrawn) The cell-line of claim 51, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

53. (Withdrawn) The cell-line of claim 47, wherein said stem cells are mesenchymal stem cells.

54. (Withdrawn) A method of increasing sensitivity of stem cells to a chemoattractant, the method comprising, upregulating an expression or activity of at least one endogenous MMP of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

55. (Withdrawn) A method of increasing sensitivity of stem cells to a chemoattractant in a subject in need, the method comprising, administrating said patient with at least one matrix metalloprotease or an active portion thereof.

56. (Withdrawn) The method according to claim 55, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

57. (Withdrawn) The method according to claim 56, wherein said matrix metalloprotease is selected from a group consisting of MMP-2, and MMP-9.

58. (Withdrawn) A method of generating stem cells suitable for transplantation, the method comprising:

(a) collecting stem cells; and

(b) exposing said stem cells to MMP or an active portion thereof.

59. (Withdrawn) A pharmaceutical composition comprising at least one matrix metalloprotease or an active portion thereof for treating a disorder requiring cell or tissue replacement.

60. (Withdrawn) A pharmaceutical composition according to claim 59, wherein wherein said matrix metalloprotease is selected from a group consisting of MMP-2, and MMP-9.

61. (Withdrawn) A pharmaceutical composition according to claim 60, wherein wherein said matrix is MMP-2.

62. (Withdrawn) A pharmaceutical composition according to claim 60, wherein wherein said matrix is MMP-9.

Exhibit B

Listing of claims as presented in Amendment filed October 12, 2009:

1. (Withdrawn) A method of increasing sensitivity of stem cells to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

2. (Withdrawn) The method of claim 1, wherein said at least one chemoattractant receptor is CXCR4.

3. (Withdrawn) The method of claim 1, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

4. (Withdrawn) The method of claim 1, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

5. (Withdrawn) The method of claim 1, wherein the stem cells are hematopoietic stem cells.

6. (Withdrawn) The method of claim 5, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

7. (Withdrawn) The method of claim 6, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

8. (Withdrawn) The method of claim 1, wherein the stem cells are mesenchymal stem cells.

9. (Withdrawn) The method of claim 1, wherein said exposing the stem cells to said matrix metalloprotease or said active portion thereof, is effected by:

(i) expressing a polynucleotide encoding said matrix metalloprotease or an active portion thereof in the stem cells; and/or

(ii) contacting the stem cells with said matrix metalloprotease or an active portion thereof.

10. (Withdrawn) A method of treating a disorder requiring cell or tissue replacement, the method comprising providing to a subject in need thereof a therapeutically effective amount of stem cells treated with a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells, thereby treating the disorder requiring cell or tissue replacement in the subject.

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20. (Withdrawn) The culture medium of claim 18, further comprising serum or serum replacement.

21. (Withdrawn) The culture medium of claim 18, further comprising an agent selected from the group consisting of SCF, HGF and IL-6.

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30. (Currently amended) A method of generating stem cells suitable for transplantation, the method comprising:

(a) collecting stem cells;

(b) exposing said stem cells to ~~a~~ an exogenous matrix metalloprotease or an active portion thereof; and

(c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof~~above a predetermined threshold~~, to thereby generate stem cells suitable for transplantation.

31. (Original) The method of claim 30, wherein collecting said stem cells is effected by:

(i) a stem cell mobilization procedure; and/or

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32. (Original) The method of claim 30, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

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35. (Original) The method of claim 34, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

36. (Original) The method of claim 34, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

37. (Withdrawn) The method of claim 30, wherein said stem cells are mesenchymal stem cells.

38. (Currently amended) The method of claim 30, wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof, is effected by:

(i) expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells; and/or

(ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof.

39. (Currently amended) The method of claim 30, wherein said isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof~~above said predetermined threshold~~ is effected by FACS.

40. (Withdrawn) The method of claim 31, further comprising determining homing capabilities of said stem cells having CXCR4 levels above said predetermined threshold following step (c).

41. (Withdrawn-Currently amended) A nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloprotease~~metalloportease~~ or an active

portion thereof and an inducible cis-acting regulatory element for directing expression of said polynucleotide in cells.

42. (Withdrawn) The nucleic acid construct of claim 41, wherein said inducible cis-acting regulatory element is a shear stress activation element.

43. (Withdrawn-Currently amended) The nucleic acid construct of claim 41, further comprising a second polynucleotide sequence being translationally fused to said first polynucleotide sequence, said second polynucleotide sequence encoding a signal peptide capable of directing secretion of said matrix metalloprotease~~metalloportease~~ or said active portion thereof out of said cells.

44. (Withdrawn) The nucleic acid construct of claim 41, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

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47. (Withdrawn) A cell-line comprising stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease.

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51. (Withdrawn) The cell-line of claim 50, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

52. (Withdrawn) The cell-line of claim 51, wherein said hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells.

53. (Withdrawn) The cell-line of claim 47, wherein said stem cells are mesenchymal stem cells.

54. (Withdrawn) A method of increasing sensitivity of stem cells to a chemoattractant, the method comprising, upregulating an expression or activity of at least one endogenous MMP of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

55. (Withdrawn) A method of increasing sensitivity of stem cells to a chemoattractant in a subject in need, the method comprising, administrating said patient with at least one matrix metalloprotease or an active portion thereof .

56. (Withdrawn) The method according to claim 55, wherein said matrix metalloprotease is selected from the group consisting of MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14.

57. (Withdrawn) The method according to claim 56, wherein said matrix metalloprotease is selected from a group consisting of MMP-2, and MMP-9.

58. (Withdrawn) A method of generating stem cells suitable for transplantation, the method comprising:

(a) collecting stem cells; and

(b) exposing said stem cells to MMP or an active portion thereof.

59. (Withdrawn) A pharmaceutical composition comprising at least one matrix metalloprotease or an active portion thereof for treating a disorder requiring cell or tissue replacement.

60. (Withdrawn-Currently amended) A pharmaceutical composition according to claim 59, wherein ~~wherein~~ said matrix metalloprotease is selected from a group consisting of MMP-2, and MMP-9.

61. (Withdrawn-Currently amended) A pharmaceutical composition according to claim 60, wherein ~~wherein~~ said matrix is MMP-2.

62. (Withdrawn-Currently amended) A pharmaceutical composition according to claim 60, wherein ~~wherein~~ said matrix is MMP-9.